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Supplementary appendix 2

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

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SUPPLEMENTAL APPENDIX

Contents

Supplemental Methods

Trial Oversight

A DSMB provided independent oversight of the trial. The DSMB was responsible for assessing: (1) baseline comparability between groups; (2) participant accrual rate and retention; (3) data quality with special emphasis on eligibility data; and (4) patient safety. The DSMB made recommendations regarding study continuation, protocol modification, and review of additional data. The DSMB reviewed planned interim analyses performed when the study reached 50%, and determined that interim analyses at 75% enrolment were not needed due to a lack of safety concerns and the speed of enrolment.

Detailed Inclusion and Exclusion Criteria

Inclusion Criteria:

1) Age 18 years or older
2) Hospitalization with a suspected diagnosis of COVID-19, based on: (a) A compatible clinical presentation with a positive laboratory test for SARS-CoV-2, or (b) Considered by the primary team to be a Person Under Investigation due to undergo testing for COVID-19 in addition to compatible pulmonary infiltrates on chest x-ray (bilateral, interstitial or ground glass opacities)
3) Use of ACEI or ARB as an outpatient prior to hospital admission

Exclusion Criteria:

1) Negative laboratory test for SARS-CoV-2
2) Systolic blood pressure <100 mmHg.
3) Systolic blood pressure > 180 mmHg or >160 if unable to substitute ACEIs/ARBs for another antihypertensive class, per the investigator's discretion.
4) Diastolic blood pressure > 110 mmHg
5) Individuals with a history of heart failure in whom: (a) left ventricular systolic function is not known (no EF assessment available); (b) the EF is known to be <40% as per the last available 2D echo; (c) in whom the EF was >40% as per the last available echocardiogram but the there was a significant interim clinical event likely to be associated with a reduction in LV EF (such as an ST-elevation myocardial infarction or chemotherapy with cardiotoxic drugs), as per investigator's assessment.
6) Serum K>5.0 mmol/L on admission.
7) Known pregnancy or breastfeeding.
8) eGFR <30 mL/min/1.73m^2
9) ≥100% increase in creatinine (to a creatinine >177 μmol/L) compared to most recent creatinine in the past six months, if available
10) Urine protein-to-creatitine ratio > 3 g/g or proteinuria > 3 g/24-hours within the past year
11) Ongoing treatment with aliskiren or sacubitril-valsartan.
12) Inability to obtain informed consent from patient.
13) Inability to read and write or lack of access to a smart phone, computer or tablet device at the time of evaluation.
14) Prisoners/incarcerated individuals

Potential participants were typically approached in the first 48-hours of admission unless they developed signs and symptoms consistent with COVID-19 during an admission for another cause. Participating in this trial did not prevent participation in other COVID-19-related interventional or observational protocols.

Informed Consent Process

To minimize exposure of the study staff to COVID-19, many sites used electronic informed consent forms. In those participants who consented electronically, the consent form was sent via email and participants attested to their consent using a deidentified participant number via an electronic REDCap survey after the informed consent process was performed via phone or video conferencing. No study interventions were initiated until the study team received either a signed informed consent form or the electronic attestation. Participants received a copy of the signed document or a REDCap attestation verification via email once they agreed to participate.

Randomized Intervention

The randomized intervention is the continuation compared with discontinuation of ACEI or ARB therapy (at the dose previously prescribed for patients during their routine care) for the duration of the hospitalization. Among participants randomized to continue these agents, clinicians are encouraged to continue the randomized treatment but are permitted to change the dose of ACEI or ARB or to discontinue these medications if a compelling clinical reason is identified, such as hypotension, hyperkalaemia, or significant acute kidney injury. If a participant is prescribed both an ACEI and an ARB prior to admission (anticipated to be rare), that individual will be randomized to continuation of one or both medications, at the clinician's discretion, or discontinuation of *both* medications. In all participants randomized to discontinuation, treating clinicians are reminded about the medication discontinuation upon discharge and are prompted to consider reinitiating the medication at that time, if clinically appropriate.

Primary Endpoint

The global rank score is a nonparametric, hierarchically ranked outcome. This approach has been used in several randomized controlled trials to facilitate evaluation of composite outcomes of binary and continuous findings accounting for both the importance of and appropriate censorship for death.[1-3] The global rank score was generated by ranking all 152 participants on a scale of 1 to 152, from worst to best clinical outcomes over the duration of the hospitalization (**Figure S1**). Participants were ranked by (1) starting with those who died, ranking participants by increasing values of days to death during the hospitalization (ordered lowest to highest); followed by (2) ranking those who underwent invasive mechanical ventilation or extracorporeal membrane oxygenation by days on invasive mechanical ventilation or extracorporeal membrane oxygenation (ordered highest to lowest); followed by (3) ranking those who underwent renal replacement therapy or received vasopressor therapy by days on renal replacement therapy or inotropic/vasopressor therapy (ordered highest to lowest); followed by (4) ranking the remainder of participants by their individual area under the curve of a modified Sequential Organ Failure Assessment (SOFA) score (**Figure S2**). The modified SOFA score includes the cardiac, respiratory, coagulation and renal domains of the SOFA score and is weighted by duration of hospitalization so that those with more severe multiorgan dysfunction and longer hospitalizations are ranked lowest (i.e. worst). The reason for the modified SOFA score is because (1) the cardiac, kidney, respiratory, and coagulation systems are those most impacted by renin-angiotensin system inhibition;[4-10] (2) these SOFA components can be reliably extracted from the electronic health record, minimising burden on the clinical team and consistent with the pragmatic nature of the trial; (3) the Glasgow comma scale and serum bilirubin, which are part of the standard SOFA score, are not typically performed daily in hospitalized patients who are not in the ICU. For the respiratory component of the SOFA score, we used peripheral capillary oxygen saturation instead of arterial oxygen saturation, an approach that has been previously applied in low-resource and non-ICU settings.[11] Use of the modified SOFA score allowed all patients in the trial to be compared to each other with regard to severity of illness, even if no adverse events took place.

Secondary and Exploratory Endpoints

Secondary endpoints:

1) Time to all-cause death
2) Length of Hospital Stay
3) Length of ICU Stay, invasive mechanical ventilation or extracorporeal membrane oxygenation
4) The Area Under the Curve of the modified SOFA (AUC SOFA) from daily measurements, weighted to account for the shorter observation period among patients who die in-hospital

Exploratory endpoints:

1) Time to ICU admission or respiratory failure requiring invasive mechanical ventilation
2) Hypotension requiring vasopressors, inotropes, or mechanical hemodynamic support (ventricular assist device or intra-aortic balloon pump)
3) Number of 28-Day Ventilator-Free Days (invasive or non-invasive)
4) Maximal change in NT-proBNP from baseline
5) Change in serum creatinine between randomization and discharge (or time of death)
6) Acute kidney injury during hospitalization (defined as KDIGO stage 2 or higher)[12]
7) Proteinuria and/or haematuria (urinalysis)

Endpoint Adjudication

A clinician panel was appointed to perform blinded adjudications of the outcome events. Each site used a standardized approach to redacting patients' electronic health records so that the adjudicators were fully blinded to the treatment assignments but were able to assess other important components of participant hospitalizations. Adjudicators were asked to recuse themselves from performing an adjudication if they were involved in the care of the participant in any way or if they became unblinded to the participant's randomization arm at any point during the study. The blinded outcome adjudicators were responsible for identifying occurrence and date of death; length of hospital stay; occurrence and duration of ICU transfer, invasive mechanical ventilation, renal replacement therapy, and vasopressor or inotropic therapy; and occurrence of other severe adverse events.

Statistical Power Comparison with Other Commonly Used Outcome Metrics in COVID-19 Trials

Using Monte Carlo simulations, we performed power calculations comparing the hierarchical outcome to 28-day ventilator-free alive days[13] and the World Health Organization (WHO) ordinal endpoint.[14] We hypothesized a therapy that reduced the median of each endpoint component by moderate effect sizes (30% or 40%) and applied this to seven differently sized populations ranging from 100 to 400 subjects. For each of the 14 combinations (two levels of efficacy x seven sample sizes), we performed Monte Carlo simulations 1000 times in which populations were randomly estimated. In each simulated population, we estimated the percent of times that each endpoint successfully rejected the null hypothesis of no treatment effect at a two-sided alpha level of 0.05. This estimates the statistical power of each endpoint in the simulated population, and this was repeated for each efficacy x sample combination. Model parameters were derived, where possible, using data in the April 24, 2020 Intensive Care National Audit and Research Centre (ICNARC) report, which hosts high quality data from > 6000 COVID-19 hospitalizations in the United Kingdom. We also utilized data from a report of COVID-19 hospitalizations in New York City to calculate several event rates.[15] We observed superior statistical power of the hierarchical endpoint compared with ventilator-free alive days and the WHO ordinal endpoint (**Figure S3**). For example, at a sample size of 200 and 30% effect size, the hierarchical endpoint achieved 90% power, compared with 40% power for ventilator-free days and 29% power for the WHO endpoint.

Data Management

The University of Pennsylvania was the Data Coordinating Centre (DCC) for the study. The DCC oversaw randomization, data entry, and DSMB meetings. The data were collected using *ad hoc* electronic case report forms. Data capture and storage were performed within the framework of the Research Electronic Data Capture (REDCap) project hosted at the University of Pennsylvania.[16,17] REDCap is a secure, web-based software platform designed to support data capture for research studies, providing (1) an intuitive interface for validated data capture; (2) audit trails for tracking data manipulation and export procedures; (3) automated export procedures for seamless data downloads to common statistical packages; and (4) procedures for data integration and interoperability with external sources.

Adverse Events

Adverse Event Reporting

The research team kept a log of all adverse events that occurred in the trial. The study team in charge of the conduct of the trial was up to date on all trainings pertaining to safety guidelines and adverse event reporting. In the context of COVID-19, the relatedness of adverse events is difficult to adjudicate, given the highly variable course of COVID-19 which may mimic the effects of ACEI continuation or withdrawal (for instance, hypotension or hypertension, worsening renal function, or cardiac decompensation). The study team remained up to date with the literature regarding the clinical manifestations of COVID-19 in order to enhance the adjudication process in real time.

Key definitions

An adverse event (AE) is any untoward medical occurrence associated with the use of a drug in a subject whether or not considered drug or biologic related. An AE can therefore be any unfavourable and unintended sign, symptom or disease temporally associated with the use of the pharmaceutical product.

Classification of AEs

A medically-qualified investigator assesses all AEs in terms of causal relationship to intervention, severity, and "expectedness" using the following guidelines.

Classification of Adverse Events for Causal Relationship to Study Interventions	
Not related	There is not a reasonable causal relationship to the investigational product and the adverse event
Unlikely related	No temporal association or the cause of the event has been identified, or the drug or device is unlikely to be implicated, but there is a low likelihood that a causal relationship exists.
Possibly related	There is reasonable evidence to suggest a causal relationship between the drug and adverse event.
Definitely Related	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely.

The severity was classified as follows:

Classification of Adverse Events Regarding Severity Scale	
1	Mild AE. Awareness of sign, symptom, or event, but easily tolerated; no treatment required
2	Moderate AE. Discomfort enough to cause interference with usual activity and may warrant intervention. In the latter scenario, AE responds to treatment
3	Severe AE. Incapacitating, limiting usual/normal activities or significantly affects clinical status requiring hospitalization or prolongation of hospitalization.

Serious Adverse Events (SAE): An adverse event or suspected adverse reaction was considered serious if the investigator or sponsor believed any of the following outcomes may have occurred:

- Death
- Life-threatening AE: Places the subject at immediate risk of death at the time of the event as it occurred. It does not include an AE that, had it occurred in a more severe form, might have caused death.
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Inpatient hospitalization or, more relevant for our trial, prolongation of hospitalization.
- Congenital anomaly or birth defect.
- Important medical events that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition above.

This determination was based on the opinion of either the investigators or DSMB.

Expectedness: The expectedness of an AE was determined based on known associations with COVID-19 or anticipated from the pharmacological properties of the drug.

The following AEs were expected, disease-related events in patients with COVID-19

1. Arrhythmias, including sinus tachycardia, ventricular arrhythmias and atrial fibrillation
2. Acute coronary syndromes with or without coronary stenoses of coronary angiography
3. Myocarditis or worsening cardiac function
4. Shortness of breath, pneumonia, acute respiratory distress syndrome and respiratory failure
5. Fever
6. Leukopenia or leukocytosis, thrombocytopenia
7. Worsening renal (resulting in worsening electrolyte abnormalities, including hyperkalaemia) and liver function
8. Worsening cognitive function
9. Coagulopathy, thrombosis, embolus, or limb ischemia
10. Hypotension or hypertension

11. Diarrhea, nausea, or vomiting
12. Anosmia (loss of sense of smell), which has been reported to occur with COVID-19.

Protocol Deviations

One patient with an eGFR of 26 mL/min/1.73m^2 was enrolled due to a miscalculation of the eGFR. This deviation did not result in harm to the participant. One participant was randomized twice (to the same arm) and one participant was randomized to the incorrect sex stratum. Neither of these deviations affected arm allocation; both participants were the last participant enrolled in their respective stratum, such that these deviations did not affect the randomized assignment of subsequent participants. None of these deviations were felt to have a substantial impact on data integrity.

Four weeks following enrolment of the final participant, there were two participants whose ongoing hospitalizations with COVID-19 were expected to be prolonged for several more weeks. Due to the need to determine the results of the trial in a timely manner to facilitate medical decision-making during the COVID-19 pandemic, the Executive Committee determined that the final two participants' blinded endpoint adjudications would be performed after a minimum of 28 days of hospitalization; one of these participants had been hospitalized for >60 days. As a sensitivity analysis, the DCC generated simulations of all feasible distributions of study results based on the potential rank scores and key secondary endpoints of these participants (considering the possibility of death, extended duration of mechanical ventilation or intensive care unit stay, and extended duration of hospitalization). The simulations demonstrated no clinically or statistically significant differences in the results of the primary and secondary analyses across outcome distributions. In all these simulations, there were no significant differences in the outcomes of interest between the trial arms.

Supplemental Tables and Figures

Online Table S1. Enrolment by Country

Country	Combined N (%)	Continuation (N=75)	Discontinuation (N=77)
United States	90 (59%)	45 (60%)	45 (58%)
Peru	35 (23%)	18 (24%)	17 (22%)
Argentina	9 (4%)	3 (4%)	6 (8%)
Bolivia	6 (4%)	3 (4%)	3 (4%)
Canada	5 (3%)	2 (3%)	3 (4%)
Mexico	4 (3%)	3 (4%)	1 (1%)
Sweden	3 (2%)	1 (1%)	2 (3%)

Online Table S2. Causes of Death

Cause of Death	Combined N (%)	Continuation (N=75)	Discontinuation (N=77)
All-cause death	21	11	10
Respiratory failure	16 (76%)	7 (64%)	9 (90%)
Shock	3 (14%)	2 (18%)	1 (10%)
Sudden arrhythmia	2 (10%)	2 (18%)	0 (0%)

Online Table S3. Severe Adverse Events

Severe Adverse Event	Combined N	Continuation (N=75)	Discontinuation (N=77)
Participants who experienced any severe adverse event	57 (38%)	29 (39%)	28 (36%)
All severe adverse events	151	81	70
All-cause death	21	11	10
ICU transfer	30	16	14
Worsening dyspnoea or acute respiratory distress syndrome	30	17	13
Invasive mechanical ventilation	18	10	8
Hypotension requiring hemodynamic support	18	9	8
Acute kidney injury requiring renal replacement therapy	3	2	1
Acute kidney injury, defined as >2-fold increase in creatinine[12]	6	3	3
Acute arrhythmia	9	6	3
Pulmonary embolism or deep vein thrombosis	5	4	1
Acute myocardial infarction	1	1	0
Myocarditis	3	1	2
New or worsening congestive heart failure	3	2	1
Delirium or encephalopathy	10	2	8

Online Table S4. As-Treated Sensitivity Analyses

Outcome	Continuation (N = 75)	Discontinuation (N = 77)	Treatment Effect (95% CI)	P-Value
Median (IQR) global rank score	74 (39, 113)	81 (38, 113)	7 (-18, 32)	0.66
Adjusted global rank score*			-4 (-24, 17)	0.74
All-cause death, n (%)	5 (7%)	8 (10%)	1.36 (0.44, 4.18)	0.59
Intensive care unit admission or invasive mechanical ventilation, n (%)	15 (20%)	14 (18%)	0.87 (0.43, 1.74)	0.70
Hypotension requiring hemodynamic support, n (%)	5 (7%)	7 (9%)	1.24 (0.41-3.80)	0.70
Median (IQR) length of hospitalization, days	4 (2, 8)	5 (3, 9)	1 (-1, 3)	0.53
Median (IQR) length of intensive care unit stay or invasive mechanical ventilation, days	12 (4, 15)	15 (6, 27)	4 (-11, 19)	0.59
Median (IQR) area under of the curve of the SOFA score adjusted for death	10 (3, 18)	7 (2, 19)	-3 (-8, 2)	0.19
Participants who experienced any severe adverse event prior to crossover, n (%)	11 (15%)	5 (6%)	0.42 (0.13, 1.33)	0.14

For continuous outcomes, the treatment effect represents the beta-coefficient (95% confidence interval) from unadjusted regression analyses unless otherwise specified. For binary outcomes, the treatment effect represents the hazard ratio (95% confidence interval). For intensive care unit admission or invasive mechanical ventilation, death was addressed as a competing risk.

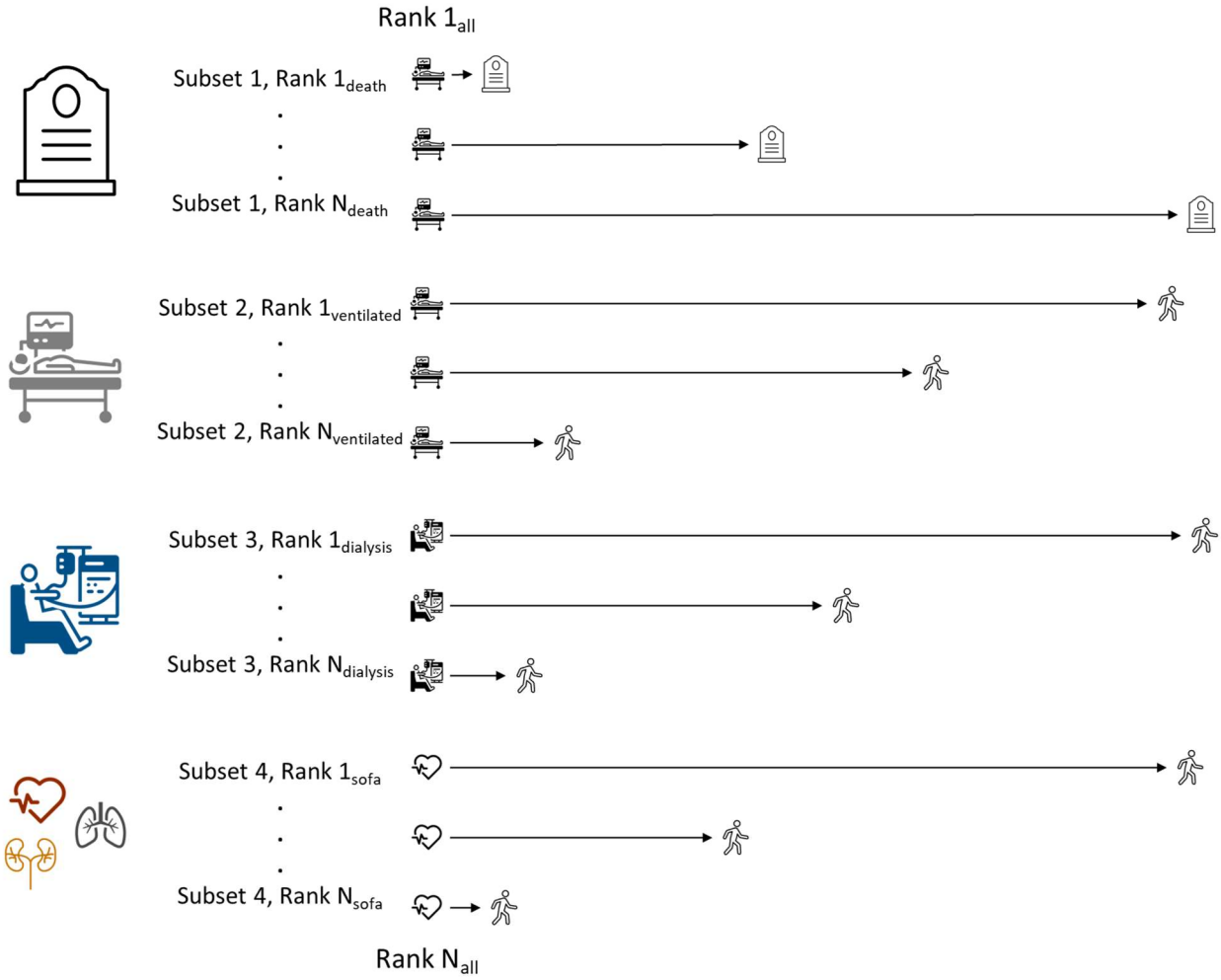
*This prespecified analysis was adjusted for age, sex, race/ethnicity, history of pre-existing heart failure, history of pre-existing chronic lung disease, and ACEI vs. ARB therapy at baseline

Online Table S5. Off-label and adjuvant COVID-19 treatments received during follow-up

Treatment	Combined N (%)	Continuation (N=75)	Discontinuation (N=77)
Remdesivir	31 (20%)	17 (23%)	14 (18%)
Hydroxychloroquine	9 (6%)	3 (4%)	6 (8%)
Systemic anticoagulation	19 (13%)	11 (15%)	8 (10%)
High-dose steroids	2 (1%)	1 (1%)	1 (1%)
Convalescent plasma	3 (2%)	2 (3%)	1 (1%)
Lopinavir/ritonavir	3 (2%)	1 (1%)	2 (3%)

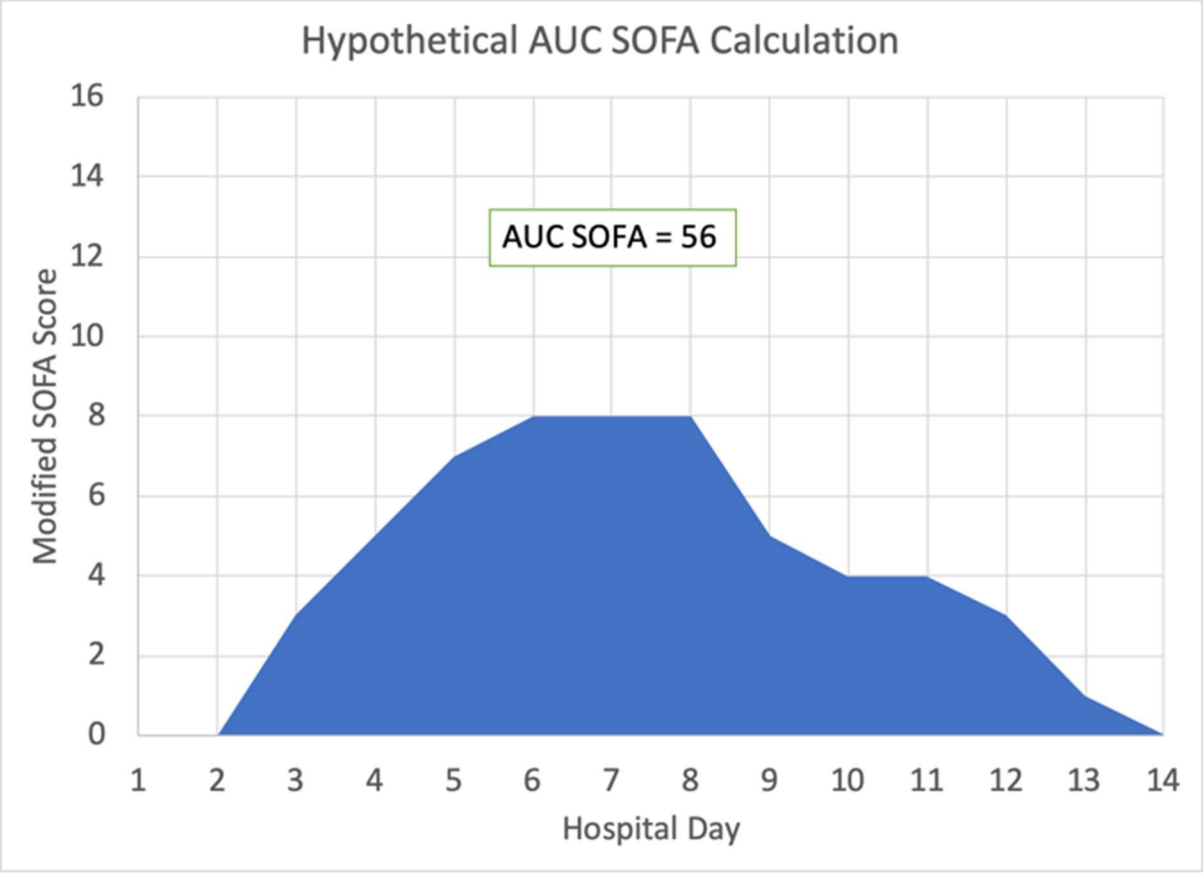
Online Figure S1. The REPLACE COVID global rank score

Subjects are ranked from worst to best outcomes by (1) days in hospital to death; (2) days on invasive mechanical ventilation or extracorporeal membrane oxygenation; (3) days on renal replacement therapy or inotropic/vasopressor therapy; and (4) area under the curve of a modified SOFA score. The figure was reprinted with permission from Cohen JB, et al. J Clin Hypertension, 2020.[10]



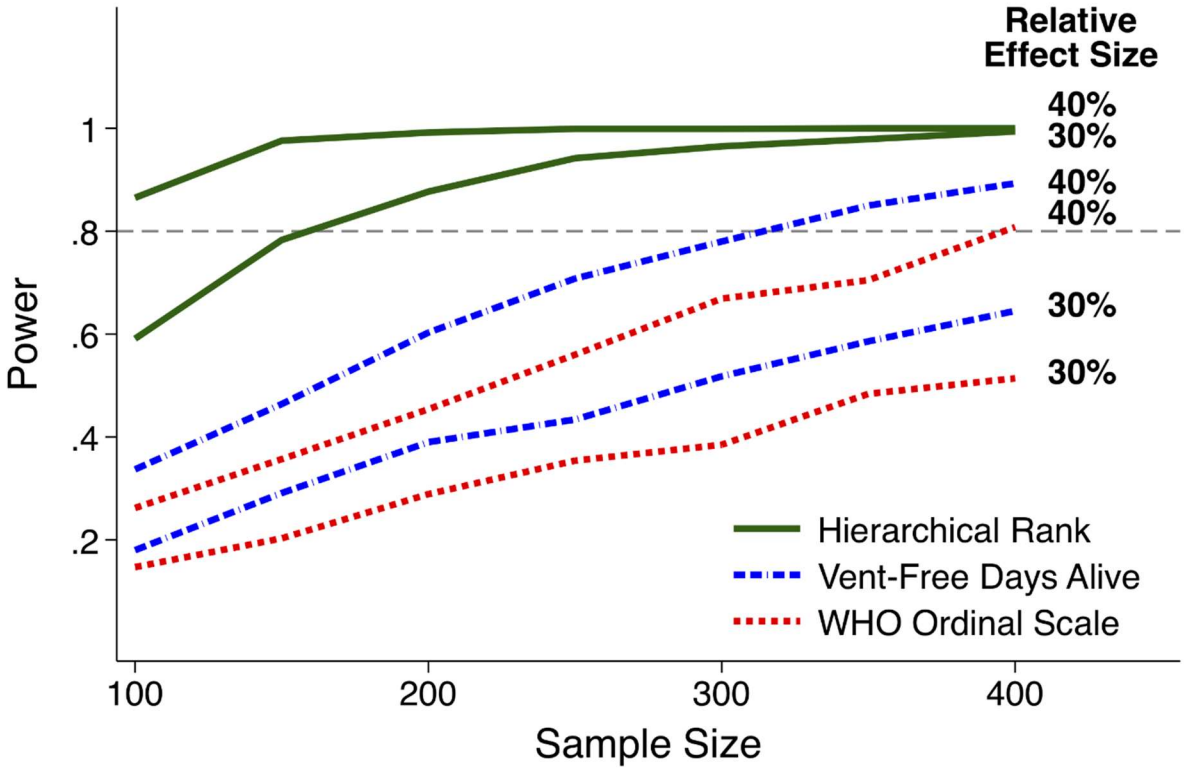
Online Figure S2. Area under the curve of the modified SOFA score

In order to summarize the SOFA score over the course of the hospitalization, we calculated the area under the curve of the modified SOFA score (AUC SOFA) from daily measurements. The AUC SOFA was ranked from highest to lowest so that lower ranks represent worse outcomes in alignment with the rest of the global rank score. Calculation of the AUC SOFA is demonstrated in this hypothetical example.



Online Figure S3. Simulated differences in statistical power across commonly used endpoints in COVID-19 trials

The hierarchical composite endpoint demonstrates superior statistical power compared with the WHO ordinal endpoint and vent-free days alive across a range of simulated effects and sample sizes.



Supplemental References

1. O'Connor CM, Whellan DJ, Fiuzat M, et al. Cardiovascular Outcomes With Minute Ventilation-Targeted Adaptive Servo-Ventilation Therapy in Heart Failure: The CAT-HF Trial. *J Am Coll Cardiol* 2017; **69**(12): 1577-87.
2. Margulies KB, Hernandez AF, Redfield MM, et al. Effects of Liraglutide on Clinical Stability Among Patients With Advanced Heart Failure and Reduced Ejection Fraction: A Randomized Clinical Trial. *JAMA* 2016; **316**(5): 500-8.
3. Felker GM, Maisel AS. A global rank end point for clinical trials in acute heart failure. *Circ Heart Fail* 2010; **3**(5): 643-6.
4. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell* 2020.
5. Ferrario CM, Jessup J, Chappell MC, et al. Effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin-converting enzyme 2. *Circulation* 2005; **111**(20): 2605-10.
6. Ocaranza MP, Godoy I, Jalil JE, et al. Enalapril attenuates downregulation of Angiotensin-converting enzyme 2 in the late phase of ventricular dysfunction in myocardial infarcted rat. *Hypertension* 2006; **48**(4): 572-8.
7. Ishiyama Y, Gallagher PE, Averill DB, Tallant EA, Brosnihan KB, Ferrario CM. Upregulation of angiotensin-converting enzyme 2 after myocardial infarction by blockade of angiotensin II receptors. *Hypertension* 2004; **43**(5): 970-6.
8. Soler MJ, Ye M, Wysocki J, William J, Lloveras J, Batlle D. Localization of ACE2 in the renal vasculature: amplification by angiotensin II type 1 receptor blockade using telmisartan. *Am J Physiol Renal Physiol* 2009; **296**(2): F398-405.
9. Senchenkova EY, Russell J, Esmon CT, Granger DN. Roles of Coagulation and fibrinolysis in angiotensin II-enhanced microvascular thrombosis. *Microcirculation* 2014; **21**(5): 401-7.
10. Cohen JB, Hanff TC, Corrales-Medina V, et al. Randomized Elimination and Prolongation of ACE Inhibitors and ARBs in Coronavirus 2019 (REPLACE COVID) Trial Protocol. *J Clin Hypertens* 2020; **00**: 1-9.
11. Grissom CK, Brown SM, Kuttler KG, et al. A modified sequential organ failure assessment score for critical care triage. *Disaster Med Public Health Prep* 2010; **4**(4): 277-84.
12. KDIGO Clinical Practice Guideline for Acute Kidney Injury. *Kidney Int Suppl* 2012; **2**(Suppl 1).
13. Yehya N, Harhay MO, Curley MAQ, Schoenfeld DA, Reeder RW. Reappraisal of Ventilator-Free Days in Critical Care Research. *Am J Respir Crit Care Med* 2019; **200**(7): 828-36.
14. WHO R&D Blueprint. Novel Coronavirus. COVID-19 Therapeutic Trial Synopsis Draft. 18 Feb 2020. https://www.who.int/blueprint/priority-diseases/key-action/COVID-19_Treatment_Trial_Design_Master_Protocol_synopsis_Final_18022020.pdf. Accessed 28 Apr 2020.
15. Richardson S, Hirsch JS, Narasimhan M, et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. *JAMA* 2020.
16. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009; **42**(2): 377-81.
17. Harris PA, Taylor R, Minor BL, et al. The REDCap consortium: Building an international community of software platform partners. *J Biomed Inform* 2019; **95**: 103208.